

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau(43) International Publication Date
12 September 2003 (12.09.2003)

PCT

(10) International Publication Number
WO 03/074024 A1

- (51) International Patent Classification⁷: A61K 9/00, 31/485 (74) Agents: MINOJA, Fabrizio et al.; Bianchetti Bracco Minoja S.r.l., Via Rossini, 8, I-20122 Milano (IT).
- (21) International Application Number: PCT/EP03/01964 (81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.
- (22) International Filing Date: 26 February 2003 (26.02.2003)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
02004786.6 1 March 2002 (01.03.2002) EP
02023589.1 23 October 2002 (23.10.2002) EP
- (71) Applicant (*for all designated States except US*): CHIESI FARMACEUTICI S.P.A. [IT/IT]; Via Palermo 26/A, I-43100 Parma (IT).
- (72) Inventors; and
- (75) Inventors/Applicants (*for US only*): DAVIES, Rebecca, Jaïne [GB/IT]; Via Palermo 26/A, I-43100 Parma (IT). GANDERTON, David [GB/IT]; Via Palermo, 26/A, I-43100 Parma (IT). LEWIS, David, Andrew [GB/IT]; Via Palermo 26/A, I-43100 Parma (IT). MEAKIN, Brian, John [GB/IT]; Via Palermo 26/A, 43100 Parma (IT). CHURCH, Tanya, Kathleen [GB/IT]; Via Palermo 26/A, I-43100 Parma (IT). BRAMBILLA, Gaetano [IT/IT]; Via Palermo, 26/A, I-43100 Parma (IT). FERRARIS, Alessandra [IT/IT]; Via Palermo, 26/A, I-43100 Parma (IT).
- (84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).
- Published:**
— with international search report
— before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*



WO 03/074024 A1

(54) Title: FORMOTEROL SUPERFINE FORMULATION

(57) Abstract: The present invention relates to a pharmaceutical formulation for use in the administration of a long-acting β_2 -agonist by inhalation. In particular this invention relates to a chemically stable highly efficient formoterol HFA solution formulation to be administered by pressurised metered dose inhalers (pMDIs) characterized by a deep lung penetration. The invention also relates to methods for the preparation of said formulation and to its use in respiratory diseases such as asthma and chronic obstructive pulmonary disease (COPD).

FORMOTEROL SUPERFINE FORMULATION**Field of the invention**

The present invention relates to a pharmaceutical formulation for use in the administration of a long-acting β_2 -agonist by inhalation.

Background of the invention

5 Asthma is a disease which is becoming more prevalent and is the most common disease of childhood. It can be identified by recurrent wheeze and intermittent air flow limitation. Despite many advances in its understanding, said pathology remains a poorly understood and often poorly treated disease. Previously, contraction of airway smooth muscles has been regarded as the
10 most important feature of asthma. Recently there has been a marked change in the way asthma is managed, stemming from the fact that asthma is recognized as a chronic inflammatory disease. Uncontrolled airway inflammation may lead to mucosal damage and structural changes giving irreversible narrowing of the airways and fibrosis of the lung tissue. Therapy should therefore be
15 aimed at controlling symptoms so that normal life is possible and at the same time provide basis for treating the underlying inflammation.

Another respiratory disease whose incidence is steadily increasing throughout the world is chronic obstructive pulmonary disease (COPD). Most patients with COPD have acquired their lung disease through smoking
20 cigarettes. Depending upon trends in tobacco smoking, it is set to rise to fifth most prevalent cause of disability, worldwide by 2020 (Leckie M et al *Exp Opin Invest Drugs* 2000, 9, 3-23).

Chronic obstructive pulmonary disease (COPD) is defined as a disease state characterized by the presence of airflow obstruction due to chronic
25 bronchitis or emphysema.

Chronic bronchitis is characterized by excessive secretion of bronchial

CONFIRMATION COPY

mucus, whereas emphysema denotes abnormal, permanent enlargement of air spaces distal to the terminal bronchiole, with destruction of their walls and without obvious fibrosis (American Toracic Society). Each condition is treated as specific diseases.

- 5 Chronic obstructive bronchiolitis is due to obstruction of the peripheral airways as a result of inflammation in the bronchioles.

β_2 -Adrenoceptor agonists have been the mainstay of treatment for asthma for many years in view of their prompt bronchodilation effects. Previous researches have also shown that β_2 -agonists have potent anti-
10 inflammatory capabilities, e.g. represented by suppression of release of the pro-inflammatory cytokines.

 The first generation drugs such as salbutamol or fenoterol were characterized by a relatively short duration of action which has been considered as a disadvantage particularly for patients with nocturnal asthma.
15 Moreover, they have limited effects in COPD, since this disease involves 'irreversible' airways obstruction. The development of longer acting β_2 -agonists such as formoterol, salmeterol and TA 2005 has therefore been heralded as a major new development in the treatment of asthma. According to some authors, long-acting β_2 -agonists (LABAs) may have acute anti-
20 inflammatory activity in vivo (Johnson M *Clin Exp Allergy* 1992, 22, 177-181; Stelmach I et al *Ann Allergy Asthma Immunol* 2002, 89, 67-73). These drugs are a new interesting therapeutic option for patients with chronic obstructive pulmonary disease (COPD) as well since they have been shown to significantly improve lung function and symptom control.

- 25 β_2 -Adrenergic agonists can also stimulate alveolar fluid clearance in several animal species and in ex vivo rat and human lungs. In view of these findings beta-adrenergic agonist therapy has been proposed as a possible

treatment for accelerating the resolution of pulmonary oedema in patients with acute pulmonary oedema (Sacuma T et al *Am J Respir Crit Care Med* 1997, 155, 506-512). Treatment with β_2 -agonists may also increase the secretion of surfactant and perhaps exert an anti-inflammatory effect, thus helping to
5 restore vascular permeability of the lung (Ware L et al *New Eng. J Med* 2000, 342, 1334-1349).

Drugs intended for the treatment of lung diseases such as asthma and COPD are currently administered by pulmonary delivery which relies on inhalation of an aerosol through the mouth and throat so that the drug substance
10 can reach the lung. They can be administered as aqueous or hydroalcoholic formulations through a nebuliser, as dry powders by means of Dry Powder Inhalers or in halogenated hydrocarbon propellants. The propellant-based systems require suitable pressurized metered-dose inhalers (pMDIs) which release a metered dose of medicine upon each actuation. The relevant
15 formulations can be in the form of solutions or suspensions. Solution formulations, with respect to suspensions, do not present problems of physical stability of the suspended particles and so could guarantee a higher dose uniformity and reproducibility. As far as the type of propellant is concerned, hydrofluoroalkanes [(HFAs) known also as hydro-fluoro-carbons (HFCs)] would
20 be mandatory propellants as chlorofluorocarbons (known also as Freons or CFCs), which were for many years the preferred propellants aerosols for pharmaceutical use, have been implicated in the destruction of the ozone layer so their use is being phased out. In particular, 1,1,1,2-tetrafluoroethane (HFA 134a) and 1,1,1,2,3,3,3-heptafluoropropane (HFA 227) have been acknowledged to be
25 the best candidates for non-CFC propellants and a number of pharmaceutical aerosol formulations using such HFA propellant systems have been disclosed.

In developing a therapeutic aerosol, the aerodynamic size distribution of

the inhaled particles is the most important variable in defining the site of droplet or particle deposition in the lungs of the patient; in short, it will determine whether drug targeting succeeds or fails. See P. Byron, "Aerosol Formulation, Generation, and Delivery Using Nonmetered Systems,"
5 "Respiratory Drug Delivery, 144-151,144 (CRC Press, 1989).

Thus, a prerequisite in developing a therapeutic aerosol is a preferential particle size.

When the formulation is in the form of suspension, the particle size of the cloud is dominated by the particle size of the suspended drug, defined by
10 the milling/micronization process. When the formulation is in the form of solution, the volumetric contribution of suspended drug particles is absent and much finer liquid droplets clouds, largely defined by the drug concentration in the solution, are generated.

Solid particles and/or droplets in an aerosol formulation can be
15 characterized by their mass median aerodynamic diameter (MMAD, the diameter around which the mass aerodynamic diameters are distributed equally).

Particle deposition in the lung depends largely upon three physical mechanisms:

- i) impaction, a function of particle inertia;
- 20 ii) sedimentation due to gravity; and
- iii) diffusion resulting from Brownian motion of fine, submicrometer (< 1 microns) particles. The mass of the particles determines which of the three main mechanisms predominates.

For aerosol therapy of drugs which topically act on the smooth muscle
25 of the conducting airways, and in particular for β_2 -agonists, it has been reported in the past that particles should preferentially deposit in the upper-to mid-pulmonary region (bronchiole region), so they should have a MMAD of

about 1.5(2.0) to about 5.0 microns, preferably approximately 3 microns (Zanen P et al *Int J Pharm* 1994, 107, 211-217; *Int J Pharm* 1995, 114, 111-115; *Thorax*, 1996, 51, 977-980).

In fact, particles having aerodynamic diameters of greater than about 5
5 microns generally do not reach the lung since they tend to impact the back of the throat and are swallowed and possibly orally absorbed, while particles smaller than 1.5 (2.0) micron, i.e., about 0.5 to about 2 microns, capable of reaching the alveolar region, have been considered undesirable because they can be absorbed into the bloodstream and might enhance the undesired systemic effects of the
10 drugs. Particles having diameters smaller than about 0.5 microns have been generally considered as not therapeutically useful as they can be exhaled.

Accordingly, pMDI formulations of β_2 -agonist have traditionally been formulations able to deliver particles whose larger fraction is comprised between 2 and 5 microns and the amount of those below 1 micron is very
15 limited since the former are small enough to reach the upper-to mid-pulmonary region, but are too large to reach the alveoli. This is also the inherent particle size of the formulation in the form of suspensions as conventional micronization (air-jet milling) of pure drug substance can reduce the drug particle size to about 2-3 microns.

20 On the other hand, it is known that the density of the beta-adrenergic receptors is higher in the distal tract of the bronchioles (Barnes P et al *Am Rev Respir Dis* 1983, 127, 758-762), a region which is better reached by smaller particles. Moreover inflammation in asthma is not merely confined to the large central airways but also extends to small peripheral airways. The eosinophilic
25 inflammation process which has been seen to be associated to asthma concerns both the bronchial and the alveolar districts (Wang S *J Immunol* 2001, 166, 2741-2749). Recently, Martin R in *J Allergy Clin Immunol* 2002, 109 (Supl 2),

447-460 reported that distal lung diseases appear to increase the risk of recurrent asthma exacerbation, while disease-related anatomic changes in the small airways of the distal lung are prominent in fatal asthma. In this respect, in his opinion, the administration of drug with particles of a diameter of about 1
5 micron (referred as "extrafine" aerosols) could be advantageous. The clinical significance of distal lung disease makes this region an important therapeutic target so particles able to reach and deposit into such region could better contribute to the management of the disease. It has been also reported that, among the particles smaller than 0.5 micron, those with a diameter less or equal
10 than 0.3 micron, preferably between 5 and 300 nm, can be deposited in the alveolar region of the lung by sedimentation. This range of particle has been referred to in the literature as "ultrafine" particles.

"Ultrafine" particles generated from di-2-ethylhexyl sebacate (DEHS) as a model, have also been reported to have a good airway penetration
15 (Anderson P et al *Chest* 1990, 97, 1115-1120). Therefore medicinal aerosol particles having a diameter $< 0.1 \mu\text{m}$ can be particularly effective in case of airway obstruction in asthmatic subjects wherein the pathology is associated with mucus hypersecretion which hinders the diffusion of the drug or in patients affected by obstructive lung diseases such as COPD. Intuitively
20 indeed, one would expect the reduction in the lumen of airways by mucus and permanent constriction would require finer clouds for perfusion.

In virtue of the inherent anti-inflammatory properties of LABAs, relevant formulations capable of delivering a significant fraction of fine particles would be expected to be of great advantage in patients affected by
25 broncho-pulmonary obstructive diseases. Amirav I et al in *J Nucl Med* 2002, 43, 487-491 emphasize the need for improvement in aerosol delivery by targeting narrow peripheral airways with superfine aerosols in the treatment of

inflammation airways diseases and in particular in acute bronchiolitis.

Formoterol, {(R,R)-(±)-N-[2-hydroxy-5-[1-hydroxy-2-[[2-(4-methoxy-phenyl)-1-methylethyl]amino]ethyl]-phenyl]formamide} is a selective β_2 -receptor agonist, exerting, upon inhalation, a prolonged bronchodilation up to
5 12 hours. It is currently marketed as CFC formulation (Foradil®).

In view of the above considerations, it would be highly advantageous to provide highly efficient formoterol formulation to be administered by pMDI characterized by a deeper lung penetration wherein, unexpectedly, the systemic exposure is not significantly higher than that of the formulations
10 currently on the market.

Description of the invention

The object of the present invention is to provide a pharmaceutical aerosol solution formulation to be administered by pMDI, having a suitable shelf-life for pharmaceutical use, comprising formoterol as active ingredient, a HFA
15 propellant and a suitable amount of co-solvent wherein the active ingredient is completely dissolved in the propellant-cosolvent system and the amount of residual water is less than 1500 ppm on the total weight of the formulation. Said solution is able of providing on actuation of the formulation a fraction of particles equal or less than 1.1 micron of at least 30% as defined by the content
20 stages S6-AF of an Andersen Cascade Impactor relative to the total amount of the fine particle dose collected in the stages S3-AF of the impactor.

The formulation of the invention is able to deliver a significant fraction of particles having a diameter equal or less than 1.1 micron, comprising both extrafine particles, according to the definition of Martin R in *J Allergy Clin*
25 *Immunol* 2002, 109 (Suppl 2), 447-460 and particles having a diameter equal or less than 0.3 micron (ultrafine particles, according to the definition of other authors). By virtue of these characteristics the formulation of the invention

will be hereinafter referred to as superfine formulation.

In the prior art sub-micron aerosol formulations (including HFA formulations) have only been reported as microemulsions containing surface active agents such as lecithin (WO 01/78689, WO 00/27363; Dickinson P et al
5 *J Drug Target* 2001, 9, 295-302).

As a preferred aspect of the present invention, we provide a pharmaceutical aerosol formulation comprising 0.003-0.192% w/v formoterol or one of its pharmaceutically acceptable salt such as fumarate as active ingredient in solution in a liquefied HFA propellant and a co-solvent preferably
10 selected from a pharmaceutically acceptable alcohol, characterized in that the fraction of particles equal or less than 1.1 micron is higher or of at least 30% and the content of humidity as determined by Karl-Fischer method is less than 1500 ppm. Advantageously the pH of the formulation is to between 2.5 and 5.0 as determined in the model vehicle system reported in EP 1157689.

15 It has been surprisingly found that following the administration of formoterol solution formulations with a significant fraction of particles of or below 1.1 micron the plasma levels of the active ingredient in the earlier phase of absorption compare to those of the CFC reference formulation on the market (Foradil) which has a small fraction of particles below 1.1 micron.

20 Moreover, it has been found that the total systemic exposure corresponding to the fraction of drug absorbed through the lung plus the amount swallowed and absorbed through the gut is slightly inferior to that of the reference formulation, making the formulation of the invention potentially better tolerated.

25 A low systemic exposure of formoterol is particularly advantageous, since the extent of drug absorbed into the blood stream is responsible of the side effects on the cardiovascular system.

As reported by the applicant in EP1157689, through the adjustment of the apparent pH it is possible to dramatically improve the chemical stability of formoterol in solution in a HFA propellant and a cosolvent. The addition of a low amount of isopropyl myristate may further improve the chemical stability of the compound.

It has now been found, as demonstrated in Example 3, that formoterol in this kind of formulation is extremely sensitive to the residual humidity and for amount of water higher than 1500 ppm on the total weight of the formulation its content decreases to such a level (less than 90% w/w) which is not longer acceptable for pharmaceutical purposes. The influence of a residual water content on the chemical stability of the active ingredient is particularly dramatic in high efficiency superfine formulations lacking of isopropyl myristate.

In the prior art HFA solution formulations of β_2 -agonists for aerosol delivery through pressurized metered-dose inhalers have been disclosed.

WO 94/13262 in the name of Boehringer Ingelheim provides aerosol solution formulations comprising a medicament, an HFC propellant, a cosolvent and an inorganic or an organic acid as a stabiliser for preventing the chemical degradation of the active ingredient. Most examples relate to ipratropium bromide, an anticholinergic drug. Although formoterol is cited among other active ingredients, no example is reported. As far as β_2 -agonists are concerned, only formulations containing fenoterol, a short acting derivative not chemically related to formoterol are exemplified. Furthermore, apart from ipratropium bromide, in WO 94/13262 no guidance is given with respect to the amount of acid which has to be added in order to stabilise the medicaments without compromising the stability of the whole composition in the can. The only hint can be found on page 5, lines 15 to 16 which says that an amount of inorganic acid should be added to obtain a pH value from 1 to 7,

so a very broad and generic range. As far as the water content is concerned, in the application it is stated that a small amount of water (up to about 5% by weight) may also be present in the propellant/cosolvent system. In the case of ipratropium bromide, it is reported that addition of 1% water reduces the decomposition due to dehydration. The document is silent about the effects of water on β_2 -agonists and especially about the effect that an amount of residual water higher than 1500 ppm might have on the chemical stability of formoterol in solution in the propellant/cosolvent system.

WO 98/34596 in the name of 3 M refers to solution formulations containing a propellant and a physiologically acceptable polymer which could help the solubilisation and the stability as well of the active ingredients.

WO 98/34595 in the name of Jago Research refers to aerosol formulations in the form of solutions or suspensions in which the propellant is a mixture of a HFA and carbon dioxide. The presence of carbon dioxide can improve either physical and chemical stability of active compounds. Formoterol is cited among the active compounds which can be used but no examples are reported.

WO 00/06121 in the name of Jago Research refers to propellant mixtures for aerosol containing dinitrogen monoxide and a hydrofluoroalkane in the preparation of suspension and solution aerosols. The use of dinitrogen monoxide may improve the stability at storage of oxidation-sensitive active ingredients. As far as LABAs such as formoterol fumarate and salmeterol xinafoate, only examples referred to suspensions are reported.

WO 99/65460 in the name of Baker Norton claims pressurised MDI's containing stable formulations of a β_2 -agonist drug in suspension or solution. Examples refer to solutions of formoterol fumarate containing an HFA propellant and ethanol as a co-solvent, filled in conventional aluminium or

plastic coated glass cans. Samples stored under accelerated conditions (40°C, 75% relative humidity) for a very short period, one month, exhibited about 10% loss of drug. According to the pharmaceutical guideline ICH Q1A "Stability Testing of new Active Substances (and Medicinal Products)" of
5 October 1993, a 5% change in assay of the active ingredient from its initial value does not meet the criteria of acceptance. Moreover, even said document is silent about the dramatic effect of residual water on the chemical stability of formoterol and its salts.

In WO 98/56349 the applicant described solution compositions for use
10 in an aerosol inhaler, comprising an active material, a propellant containing a hydrofluoroalkane (HFA), a co-solvent and further comprising a low volatility component to increase the mass median aerodynamic diameter (MMAD) of the aerosol particles on actuation of the inhaler. In some cases a small quantity of water may be added to the composition to improve the solution of the active
15 material and/or the low volatility component in the cosolvent.

In EP 1157689 the applicant disclosed aerosol pharmaceutical compositions comprising a β_2 -agonist belonging to the class of phenylalkylamino derivatives in solution in a HFA propellant, a co-solvent whose apparent pH has been adjusted to between 2.5 and 5.0 in order to
20 guarantee an adequate shelf-life. In a particular embodiment of the invention, isopropyl myristate (IPM) as a low-volatility is added in order to either increase the MMAD of the aerosol particles and further improving the stability of the formulation. As far as the role of water is concerned, it is only generically stated that humidity, in the case of certain active ingredients such as formoterol,
25 could be detrimental to the (chemical) stability during storage. Formoterol-based HFA 134a solution formulations containing 12% w/w ethanol with or without 1.0% w/w IPM are reported in example 5. No guidance is given in EP

1157689 for further improving the stability of the relevant formulations by strictly controlling the residual amount of water, in particular when IPM, which improves the chemical stability of formoterol, is avoided. There is no preference in EP 1 157 689 for compositions containing IPM or not.

5 As mentioned above, the formulations of the invention can also comprise a further active ingredient. In particular, the addition of a corticosteroid to a long-acting β_2 -agonist gives optimal control of asthma in most patients and relevant fixed combinations are increasingly used as a convenient controller in patients with persistent asthma. It has also been
10 reported that each class of drug enhances the beneficial actions of the other. In fact, corticosteroids increase the expression of β_2 -receptors and protect them against down-regulation in response to long-acting β_2 -agonist exposure, whereas β_2 -agonist may enhance the anti-inflammatory actions of corticosteroids (Barnes P et al. *Eur Respir J* 2002, 19, 182-191).

15 Accordingly, another object of the present invention is to provide highly efficient formoterol formulations further comprising a steroid. The high fraction of superfine particles of the formulation of the invention can allow both drugs to reach the small peripheral airways region in such a way as to better exercise their synergic effects in distal lung diseases (*vide supra*).
20 Moreover, in view of the aforementioned characteristics, it might be possible to develop formulations comprising fixed combinations of formoterol and a steroid wherein the latter one could be present in a lower dose, by maintaining the same therapeutic effect.

A further aspect of the present invention is to provide highly efficient
25 formoterol formulations in combination with an anticholinergic atropine-like derivative such as ipratropium bromide, oxitropium bromide and tiotropium bromide in order to provide a medicament particularly effective for the

treatment of COPD.

It is also provided a method of filling an aerosol inhaler with a composition of the invention, the method comprising:

- (a) preparation of a solution of one or more active ingredients in one
5 or more co-solvents
- (b) optionally adjusting the pH of the solution
- (c) filling of the device with said solution
- (d) crimping with valves and gassing
- (e) adding a propellant containing a hydrofluoroalkane (HFA)

10 A still further aspect of the invention comprises the use of the formoterol fully dissolved in the propellant / co-solvent system and capable of providing on actuation a fraction of at least 30% of emitted particles with an aerodynamic diameter equal or less than 1.1 microns, for the treatment of respiratory disorders such as asthma and COPD.

15 In view of its technical feature of providing on actuation a fraction of particles with an aerodynamic diameter of less than 1.1 micron, of at least 30%, the formulation of the invention can be particularly effective for the treatment of asthma, COPD and, generally, of airway obstruction conditions wherein the pathology is associated with mucus hypersecretion which hinders
20 the diffusion of the drug.

Furthermore, it may be clinically useful as a treatment to hasten the resolution of alveolar oedema and of surfactant-deficiency related diseases such as acute lung injury (ALI) and acute respiratory distress syndrome (ARDS).

25 Detailed description of the invention

The aerosol formulations of the invention comprise an HFA propellant and a co-solvent wherein the active ingredient is fully dissolved in such a way

that the formulations are able of providing on actuation a fraction of emitted particles of equal or less than 1.1 microns higher or equal to 30% as defined by the content stages S6-AF of an Andersen Cascade Impactor relative to the total fine particle dose collected in the stages S3-AF of the impactor, 5 advantageously higher than 40%, preferably higher than 50%, more preferably higher than 60%, even more preferably higher than 70%. Advantageously, the formulations of the invention are free of other excipients such as surfactants besides the solubilisation agent and the propellant.

Examples of HFA propellants include 1,1,1,2-tetrafluoroethane 10 (HFA134a) and 1,1,1,2,3,3,3-heptafluoro-n-propane (HFA227) and mixtures thereof. The preferred propellant is 1,1,1,2-tetrafluoroethane (HFA134a). An alternative propellant of interest is 1,1,1,2,3,3,3-heptafluoro-n-propane (HFA227).

The co-solvent is selected from the group of lower alkyl (C_1 - C_4) 15 alcohols, polyols, polyalkylene glycols and their combinations. Other suitable co-solvents are (poly)alkoxy derivatives including polyalkoxy alcohols, [such as 2-(2-ethoxyethoxy) ethanol available under the trademark Transcutol®].

Preferably the co-solvent is an alcohol. The preferred one is ethanol. Since the presence of water has to be avoided as much as possible, the co- 20 solvent will be even more preferably anhydrous ethanol, optionally dried on 3 Å sieves. The concentration of the co-solvent (e.g. ethanol) will vary depending on the final concentration of the active ingredients in the formulation and on the propellant. The amount of ethanol should not exceed around 40% w/w of the total weight of the formulation. Advantageously it is 25 comprised between 5 and 30% w/w, preferably between 10 and 20% w/w, even more preferably between 12 and 15% w/w.

Active ingredients which may be used in the aerosol compositions of

the invention are formoterol and stereoisomers, physiologically acceptable salts and solvates thereof.

Suitable physiological salts include chloride, bromide, sulphate, phosphate, maleate, fumarate, tartrate, citrate, benzoate, mesilate, ascorbate,
5 salicylate, acetate, succinate, lactate, glutarate or gluconate.

In one of the embodiments of the invention, we prefer to use (R,R)-(±) formoterol more preferably in the form of fumarate salt.

Said active ingredient can be used alone or in combination with steroids such as beclometasone dipropionate (BDP), flunisolide, mometasone furoate,
10 fluticasone propionate, ciclesonide, budesonide and its 22R-epimer, with anticholinergic atropine-like derivatives such as ipratropium bromide, oxitropium bromide, tiotropium bromide or with drugs useful for the management of respiratory diseases such as methylxanthines, anti-leukotrienes and phosphodiesterase inhibitors.

15 The preferred combinations concern formoterol and BDP, budesonide or its 22R-epimer.

The concentration of formoterol in the HFA formulation will depend on the therapeutic amount to be delivered preferably in one or two actuations.

In the foregoing drug concentrations are given as (w/v) and as fumarate
20 salt. The corresponding percentages as (w/w) can be calculated by determining the density of the vehicle.

The formulation according to the invention will be filled in a canister fitted with a suitable metering valve. We prefer that the formulation is actuated by a metering valve capable of delivering a volume of between 25 µl
25 and 100 µl, e.g. 50 µl or 63 µl. 100 µl is also suitable.

The concentration of formoterol will vary between 0.003 and 0.192% w/v, preferably between 0.006 and 0.048% w/v in order to deliver 3 to 48 µg,

preferably 6 or 12 μg per actuation.

For instance, for a 12 μg dose, when a 100 μl metering volume is used, the final concentration of formoterol fumarate delivered per actuation would be 0.012% w/v; where a 50 μl metering volume is used, the final
5 concentration of formoterol fumarate would be doubled, e.g. 0.024% w/v and where a 63 μl metering volume is used, which is the preferred one, the final concentration would be 0.019% w/v.

The intended dose regimen is twice or once daily, where the suitable daily dose is in the range of 6 to 48 μg .

10 The apparent pH range is advantageously between 2.5 and 5.0, preferably between 3.0 and 4.5. Strong mineral acids preferably selected from hydrochloric, nitric, phosphoric acid can be used to adjust the apparent pH, more preferably hydrochloric acid.

The amount of acid to be added to reach the desired apparent pH will be
15 pre-determined in the model vehicle reported in EP 1157689 and it will depend on the type and concentration of the active ingredient and the amount of the co-solvent. For 0.019% w/v formoterol fumarate solutions in 12% w/w ethanol and HFA 134a q.s. to about 10 ml, an amount comprised between 3.85 and 4.85 μl of 1 M HCl is advantageously added, preferably between 4.15 and
20 4.55 μl of 1 M HCl, with the optimum of 4.35 μl . In more general terms, the concentration of 1 M HCl is between 0.030% w/w and 0.045% w/w, preferably between 0.035% and 0.040% w/w on the total weight of the formulation.

The amount of water is lower than 1500 ppm, preferably lower than
25 1000 ppm, even more preferably lower than 500 ppm on the total weight of the formulation.

The formulations of the invention will be filled into canisters suitable for

delivering pharmaceutical aerosol formulations such as plastic or plastic coated glass bottle or preferably a metal can, for example an aluminium can. The formulations can also be filled in canisters having part of all of the internal surfaces made of anodised aluminium, stainless steel or lined with an inert organic coating. Examples of preferred coatings are epoxy-phenol resins, perfluorinated polymers such as perfluoroalkoxyalkane, perfluoroalkoxyalkylene, perfluoroalkylenes such as poly-tetrafluoroethylene (Teflon), fluorinated-ethylene-propylene, polyether sulfone and a copolymer fluorinated-ethylene-propylene polyether sulfone. Other suitable coatings could be polyamide, polyimide, polyamideimide, polyphenylene sulfide or their combinations.

To further improve the stability, cans having a rim with rounded edges, preferably a rolled neck or rolled-in rim, a part or full rollover rim can be used according to the teaching of the co-pending application n. WO 02/72448 .

The canister is closed with a metering valve. The metering valves are designed to deliver a metered amount of the formulation per actuation and incorporate a gasket to prevent leakage of propellant through the valve.

The gasket may comprise any suitable elastomeric material such as for example low density polyethylene, chlorobutyl, black and white butadiene-acrylonitrile rubbers, butyl rubber, neoprene, EPDM (a polymer of ethylenepropylenediene monomer) and TPE (thermoplastic elastomer). EPDM and TPE rubbers are preferred. EPDM rubbers are particularly preferred. Suitable valves are commercially available from manufacturers well known in the aerosol industry, for example, from Valois, France (eg. DF10, DF30, DF60), Bepak plc, UK (eg. BK300, BK356, BK357) and 3M-Neotechnic Ltd, UK (eg. Spraymiser). The DF31 valve of Valois, France is also suitable. Valve seals, especially the gasket seal, and also the seals around the metering chamber, will preferably be manufactured of a material which is inert to and

resists extraction into the contents of the formulation, especially when the contents include ethanol.

Valve materials, especially the material of manufacture of the metering chamber, will preferably be manufactured of a material which is inert to and
5 resists distortion by contents of the formulation, especially when the contents include ethanol. Particularly suitable materials for use in manufacture of the metering chamber include polyesters e.g. polybutyleneterephthalate (PBT) and acetals, especially PBT.

Materials of manufacture of the metering chamber and/or the valve stem
10 may be fluorinated, partially fluorinated or impregnated with fluorine containing substances in order to resist drug deposition.

Conventional bulk manufacturing methods and machinery well known to those skilled in the art of pharmaceutical aerosol manufacture may be employed for the preparation of large-scale batches for the commercial
15 production of filled canisters. Thus, for example, in one bulk manufacturing method a metering valve is crimped onto an aluminum can to form an empty canister. The medicament is added to a charge vessel and a mixture of ethanol, optionally water and liquefied propellant is pressure filled through the charge vessel into a manufacturing vessel. An aliquot of the formulation is then filled
20 through the metering valve into the canister.

In an alternative process, an aliquot of the liquefied formulation is added to an open canister under conditions which are sufficiently cold that the formulation does not vaporize, and then a metering valve crimped onto the canister.

In an alternative process, an aliquot of medicament dissolved in the
25 solubilising agent is dispensed into an empty canister, a metering valve is crimped on, and then the propellant is filled into the canister through the valve. Preferably, the processes are carried out in an inert atmosphere, for instance by

insufflating nitrogen, in order to avoid the uptake of humidity from the air.

Each filled canister is conveniently fitted into a suitable channeling device prior to use to form a metered dose inhaler for administration of the medicament into the lungs of a patient. Suitable channeling devices comprise, for example a valve actuator and a cylindrical or cone-like passage through which medicament may be delivered from the filled canister via the metering valve to the mouth of a patient e.g. a mouthpiece actuator.

In a typical arrangement the valve stem is seated in a nozzle block which has an orifice leading to an expansion chamber. The expansion chamber has an exit orifice which extends into the mouthpiece. Actuator (exit) orifice diameters in the range 0.15 - 0.45 mm especially 0.2 - 0.45 mm are generally suitable e.g. 0.25, 0.30, 0.33 or 0.42 mm. 0.22 mm is also suitable. For certain formulations it would be useful to utilize laser-drilled actuator orifices having a diameter ranging from 0.10 to 0.22 mm, in particular from 0.12 to 0.18 mm as those described in the co-pending application n. EP 1130521.6.

The use of such fine orifices also increases the duration of cloud generation and lowers its velocity. These changes facilitate the coordination of cloud generation with the slow inspiration of the patient.

Since the ingress of water into the formulation needs to be avoided, it may be desired to overwrap the MDI product in a package, preferably flexible, capable of resisting water ingress. It may also be desired to incorporate a material within the packaging which is able to adsorb any propellant and co-solvent which may leak from the canister. (e.g. a molecular sieve).

The aerodynamic particle size distribution of each tested formulation of the invention can be characterized using a Multistage Cascade Impactor according to the procedure described in European Pharmacopoeia 2nd edition, 1995, part V.5.9.1, pages 15-17. In this specific case, an Andersen Cascade

Impactor (ACI) was utilized operating at a flow rate of 28.3 l/min. Deposition of the drug on each ACI plate was determined by high pressure liquid chromatography (HPLC). Mean delivered dose was calculated from the cumulative deposition in the ACI. Mean respirable dose (fine particle dose) was obtained from the deposition on Stages 3 (S3) to filter (AF) corresponding to particles ≤ 4.7 microns, divided by the number of actuation per experiment, while mean "superfine" dose was obtained from the deposition on Stages 6 to filter corresponding to particles ≤ 1.1 microns.

Administration of the formulations of the invention may be indicated for the treatment of mild, moderate or severe, acute or chronic symptoms or for prophylactic treatment of respiratory diseases such as asthma and chronic obstructive pulmonary disease (COPD). Other respiratory disorders characterized by obstruction of the peripheral airways as a result of inflammation and presence of mucus such as chronic obstructive bronchiolitis and chronic bronchitis can also benefit of this kind of formulation.

The invention is illustrated with reference to the following examples.

Example 1 - Superfine formoterol HFA formulation

A formulation was prepared with the composition as follows:

<i>Components</i>	<i>Amounts</i>		
	Per unit		Nominal dose
		%	μg
Formoterol fumarate	1.92 mg	0.019 w/v	12
Anhydrous ethanol	1416.7 mg	12 w/w	-
HCl 1 M	4.40 mg*	0.037 w/w	-
HFA 134a (q.s. to 10.09 ml)	11808 mg	-	-

* equivalent to 4.35 μl

The formulation (120 actuations/canister, overage of 40 actuations) was

filled in standard aluminum canisters (two stage pressure filling) under pressure and fitted with a metering valve having a 63 μ l metering chamber. Two actuators were used with orifice diameter of 0.30 and 0.42 mm. Results were obtained as a mean of 2 cans.

- 5 The aerodynamic particle size distribution was determined by ACI, according to the description on page 17 lines 4 to 12.

The delivery characteristics of the formulation are reported in Table 1 in comparison with the reference CFC formulation currently available on the market (Foradil). In particular the following parameters are reported: i) 10 nominal dose: theoretical dose per single actuation; ii) delivered dose: amount of active particles deposited into the all ACI stages; iii) respirable dose (fine particle dose): amount of active particles of size equal or less than 4.7 microns (S3-AF); iv) respirable fraction (fine particle fraction): ratio between the respirable dose and the delivered dose; v) "superfine" dose: amount of active 15 particles equal or less than 1.1 microns (S6-AF); iv) "superfine" fraction: ratio between the "superfine" dose and the respirable dose.

Table 1 - Delivery characteristics of the formoterol HFA solution formulations of the Ex.1.

	Nominal Dose (μ g)	Delivered dose (μ g)	Respirable dose (μ g)	Respirable fraction (%)	Superfine dose (μ g)	Superfine Fraction (%)
Formulation Ex1 Act 0.30 mm	12	10.02	3.31	32.5	2.53	76.4
Formulation Ex 1 Act 0.42 mm	12	10.84	2.14	19.7	1.57	73.3
Foradil	12	11.1	5.70	51.4	1.18	20.7

The results show that the reference formulation upon actuation shows a higher respirable fraction, while the formulations of the invention give rise to a dramatically higher percentage of particles with a diameter equal or less than 1.1 microns, particles which are thought to better reach the distal tract of the bronchioles.

Example 2 - Pharmacokinetics study

The aim of the study was to evaluate the pharmacokinetics of formoterol in 6 healthy volunteers after single administration of the formoterol formulations of Example 1 at 120 µg dose (10 shots x 12 µg/shot) in comparison with the marketed CFC formulation (Foradil). The experimental protocol is reported as follows:

Treatments

- Foradil CFC 120 µg. (10 shots x 12 µg/shot): Reference formulation
- Formoterol/HFA orifice 0.42mm 120 µg. (10 shots x 12 µg/shot): Test formulation
- Formoterol/HFA orifice 0.30mm 120 µg. (10 shots x 12 µg/shot): Test formulation

The study was a single dose cross-over study; subjects received the drug at 8 a.m. The wash-out among different treatments was of at least 1 weeks. Patients were instructed to take 10 doses. Time 0 for each dose was defined as the time when the MDI is first actuated.

Bioanalysis

Assay of formoterol was carried out employing HPLC/MS validated method with a LOQ of 2pg/mL.

The pharmacokinetics parameters are reported in Table 2 while in Figure 1 the plasma concentration in the first two hours are shown.

Table 2 - Pharmacokinetics parameters

	Foradil CFC	Formoterol HFA of Ex.1 0.42 mm	Formoterol HFA of Ex.1 0.30 mm
C_{max} (pg ml ⁻¹)	159 ± 34	150 ± 36	158 ± 32
AUC_(0-20min) (pgml ⁻¹ *h)	35.4 ± 9,0	34.3 ± 7,3	36.5 ± 7.3
AUC_t (pgml ⁻¹ *h)	655 ± 153	611 ± 103	578 ± 98

C_{max} is the maximum plasma concentration

AUC_{0-20 min} is the area under the curve of the plasmatic levels from time
5 0 h to 20 minutes;

AUC_t is the area under the curve of the plasmatic levels from time 0 h
to the last measurable data point.

The results demonstrate that the formoterol formulations of Example 1,
despite their different particle size distribution characterized by a high fraction
10 of particles equal or less than 1.1 µm, show plasma levels in the 0 to 20 min
time interval, that reflects the amount of drug absorbed from the lung,
comparable to the reference formulation.

Surprisingly, the total systemic exposure (see Figure 1), corresponding
to the fraction of drug absorbed through the lung plus the amount swallowed
15 and absorbed through the gut, is slightly lower with the formulations of the
invention than with the reference one. This may be considered as an advantage
since for a drug that exert its activity at the lung level, a reduced systemic
exposure may translate in a decreased risk of undesired systemic effects.

In a preliminary clinical trial it was also demonstrated that the
20 formulations of Examples 1 and 2 have a bronchodilator action equivalent to
that of the reference formulation in CFC propellant and a good tolerability.

Example 3 – Effect of the residual humidity on the formoterol assay

The formulation of Example 1 filled in standard aluminum cans was

stored in different conditions (25°C, 40°C) and for different times (0, 3, 6 months).

The assay of formoterol was determined by HPLC while the water content was determined by Karl-Fischer method.

5 The results, reported in Figure 2, show an inverse linear correlation between the assay of formoterol and the residual amount of water. The numbers between brackets refer to time and temperature condition, respectively. The formoterol assay for a residual humidity lower than 1500 ppm meets the requirements of the ICH guideline Q1A, whereas for a residual
10 humidity higher than 1500 ppm, the assay decreases below 90%.

Example 4 – Stability study

A stability study on a formulation prepared according to the Example 1 was initiated storing the cans upright and inverted at 5°C.

Assays of formoterol and its main related substances (degradation
15 products) were determined by HPLC.

At twelve months the formoterol assay is higher than 95% and therefore meets the requirements of the ICH guideline Q1A. Under these storage conditions, the water content maintains below 1000 ppm.

The storage conditions are the same of that of the reference product
20 Foradil® whereas the shelf life is better, as the latter has to be kept at refrigerator temperature for maximum nine months.

CLAIMS

1. A pharmaceutical aerosol formulation to be administered by pressurized metered dose inhalers which comprises an active ingredient selected from
5 formoterol or a stereoisomer, physiologically acceptable salt and solvate thereof, in a solution of a liquefied HFA propellant and a co-solvent, characterised in that the amount of residual water is less than 1500 ppm on the total weight of the formulation.
2. A pharmaceutical formulation according to claim 1 wherein the amount
10 of residual water is less than 1000 ppm.
3. A pharmaceutical formulation according to claim 1 wherein the amount of residual water is less than 500 ppm.
4. A pharmaceutical formulation according to claims 1-3 wherein the
15 fraction of particles equal or less than 1.1 μm delivered on actuation of the inhaler is higher or equal than 30% as defined by the content of the stages S6-AF of an Andersen Cascade Impactor, relatively to the content of the stages S6-AF, according to the method referred to in the description on page 17 lines 4 to 12.
5. A pharmaceutical formulation according to claims 1-4 wherein the
20 superfine fraction is higher than 50%.
6. A pharmaceutical formulation according to claims 1-5 wherein the active ingredient is (R,R)-(\pm)-formoterol fumarate in a concentration comprised between 0.003 and 0.192 % w/v.
7. A pharmaceutical formulation according to claim 6 wherein the active
25 ingredient is in a concentration comprised between 0.006 and 0.048% w/v.
8. A pharmaceutical formulation according to any preceding claim wherein the pH is comprised between 2.5 and 5.0.

9. A pharmaceutical formulation according to claim 8 wherein the pH is comprised between 3.5 and 4.0.
10. A pharmaceutical formulation according to claims 8 and 9 wherein the pH is adjusted by adding hydrochloric acid.
- 5 11. A pharmaceutical formulation according to any preceding claim, wherein the propellant includes one or more hydrofluoroalkanes [HFAs] selected from the group comprising HFA 134a and HFA 227.
12. A pharmaceutical formulation according to any preceding claim, wherein the co-solvent is selected from the group of lower alkyl (C₁-C₄)
10 alcohols, polyols, polyalkylene glycols, (poly)alkoxy derivatives and their combinations.
13. A pharmaceutical formulation according to claim 12 wherein the co-solvent is ethanol.
14. A pharmaceutical formulation according to claim 13 wherein ethanol is
15 in anhydrous form.
15. A pharmaceutical formulation according to claims 13-14 wherein the concentration of ethanol is comprised between 10 and 20% w/w.
16. A pharmaceutical formulation according to any preceding claim filled in a canister having part or all of its internal metallic surfaces made of
20 standard aluminium, stainless steel, anodised aluminium or lined with an inert organic coating.
17. A pharmaceutical formulation according to claim 15 comprising 0.012-0.048% w/v formoterol fumarate, 12% w/w anhydrous ethanol, 0.037% w/w HCl 1 M and HFA 134a.
- 25 18. A pharmaceutical formulation according to claim 15 comprising 0.006-0.024% w/v formoterol fumarate, 12% w/w anhydrous ethanol, 0.023% w/w HCl 1 M and HFA 134a.

19. A pharmaceutical formulation according to any preceding claim comprising a further active ingredient selected from the class of steroids such as beclomethasone dipropionate, fluticasone propionate, ciclesonide, budesonide and its 22R-epimer or anticholinergic atropine-like derivatives
5 such as ipratropium bromide, oxitropium bromide, tiotropium bromide.
20. A pharmaceutical formulation according to any preceding claim filled in a pressurized metered dose inhaler overwrapped in a package capable of resisting water ingress.
21. A pharmaceutical formulation according to claim 20 wherein the
10 package further incorporates a material able to adsorb any propellant and cosolvent which may leak from the canister such as a molecular sieve.
22. A method of preparing the pharmaceutical formulations of claims 1-19, the method comprising:
- (a) preparing of a solution of one or more active ingredients in one
15 or more co-solvents;
 - (b) optionally adjusting the pH of the solution;
 - (c) filling of the device with said solution;
 - (d) crimping with valves and gassing;
 - (e) adding a propellant containing a hydrofluoroalkane (HFA).

Formoterol plasma levels in 6 healthy volunteers after inhalation of a 120 mcg dose

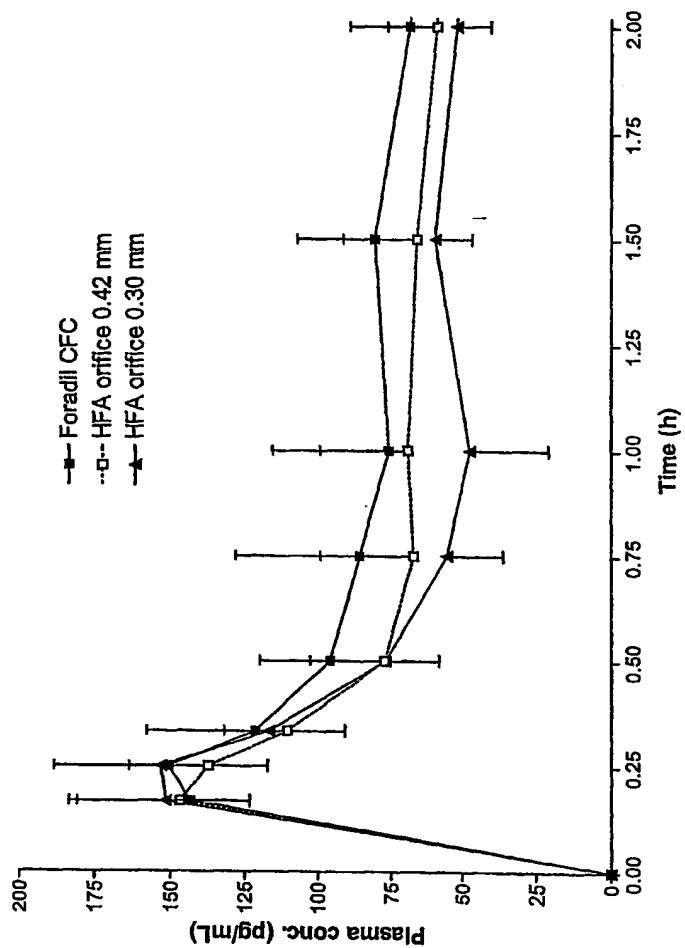
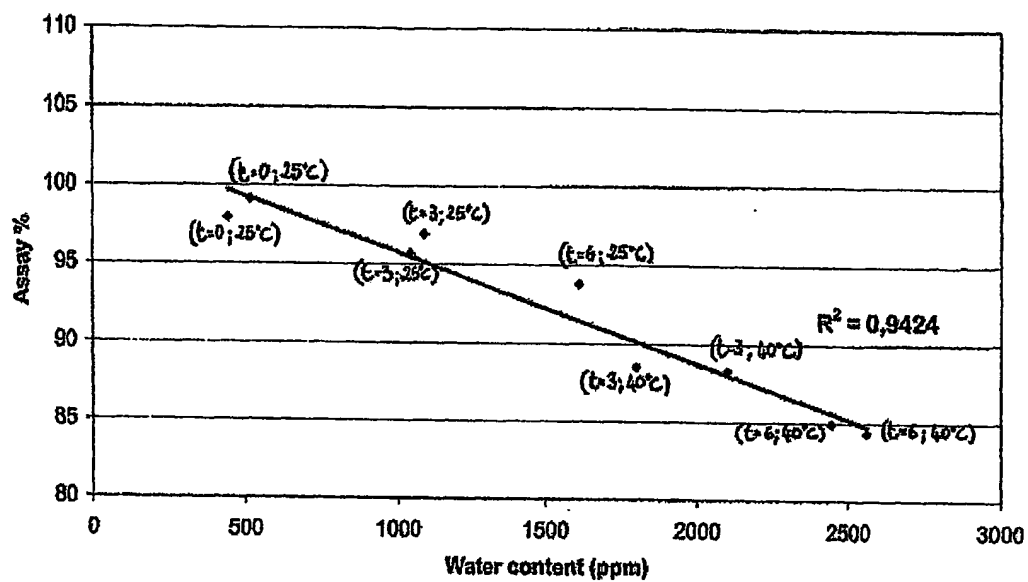


Figure 1

Figure 2

Correlation between the assay of formoterol and the residual water content in the formulation



R^2 is the correlation coefficient deriving from the regression analysis

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 03/01964

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K9/00 A61K31/485

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

WPI Data, EPO-Internal, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 6 004 537 A (CAVANAUGH KELLY A ET AL) 21 December 1999 (1999-12-21) column 2, line 28 - line 46 claims; examples	1,4, 6-16,19
X	EP 1 157 689 A (CHIESI FARMA SPA) 28 November 2001 (2001-11-28) page 1, paragraph 1 - paragraph 5 page 2, paragraph 18 - paragraph 22 examples 2-6	1,4, 6-16,19
A	US 6 150 418 A (HOCHRAINER DIETER ET AL) 21 November 2000 (2000-11-21) column 1, line 30 - line 54 examples 1-3	1-22

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

A document defining the general state of the art which is not considered to be of particular relevance

E earlier document but published on or after the international filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

G document member of the same patent family

Date of the actual completion of the international search

4 July 2003

Date of mailing of the international search report

20/08/2003

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Rankin, R

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 03/01964

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 6004537	A	21-12-1999	AU 2194900 A	03-07-2000
			BR 9916829 A	23-10-2001
			CA 2355932 A1	22-06-2000
			CZ 20012216 A3	17-04-2002
			EP 1140059 A2	10-10-2001
			HU 0200014 A2	29-06-2002
			JP 2002532418 T	02-10-2002
			PL 348809 A1	17-06-2002
			WO 0035441 A2	22-06-2000
EP 1157689	A	28-11-2001	WO 0189480 A1	29-11-2001
			EP 1157689 A1	28-11-2001
			NO 20025568 A	20-11-2002
			AU 5070100 A	03-12-2001
			CA 2411047 A1	29-11-2001
			CZ 20023835 A3	16-04-2003
			US 2002025299 A1	28-02-2002
US 6150418	A	21-11-2000	DE 19847969 A1	20-04-2000
			AT 218331 T	15-06-2002
			AU 6201999 A	08-05-2000
			BG 105391 A	30-11-2001
			BR 9914507 A	26-06-2001
			CA 2343123 A1	27-04-2000
			CN 1333682 T	30-01-2002
			CZ 20011362 A3	12-09-2001
			DE 59901669 D1	11-07-2002
			DK 1121112 T3	16-09-2002
			EE 200100224 A	17-06-2002
			WO 0023065 A2	27-04-2000
			EP 1121112 A2	08-08-2001
			ES 2178479 T3	16-12-2002
			HR 20010255 A1	30-04-2002
			HU 0103925 A2	29-05-2002
			JP 2002527473 T	27-08-2002
			NO 20011663 A	03-04-2001
			PL 348434 A1	20-05-2002
			PT 1121112 T	29-11-2002
			SI 1121112 T1	31-10-2002
			SK 4942001 A3	11-09-2001
			TR 200101096 T2	21-12-2001

Form PCT/ISA/210 (patent family annex) (July 1992)

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☐ **BLACK BORDERS**
- ☐ **IMAGE CUT OFF AT TOP, BOTTOM OR SIDES**
- ☐ **FADED TEXT OR DRAWING**
- ☐ **BLURRED OR ILLEGIBLE TEXT OR DRAWING**
- ☐ **SKEWED/SLANTED IMAGES**
- ☐ **COLOR OR BLACK AND WHITE PHOTOGRAPHS**
- ☐ **GRAY SCALE DOCUMENTS**
- ☒ **LINES OR MARKS ON ORIGINAL DOCUMENT**
- ☐ **REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY**
- ☐ **OTHER: _____**

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.